tilled for a short period to remove traces of moisture. It was then treated dropwise, at the boiling point under reflux, with a solution of 1.25 g. of aluminum isopropoxide in 15 ml. of toluene over a period of five minutes. After one-half hour of reflux, the solution was diluted with water and ether. The ethereal layer was washed with 2% sodium hydroxide solution and then water until neutral. The ether was removed and the residue was steam distilled for one hour. The solid was separated after adding a small amount of sodium chloride and chilling. The air-dried, crystalline solid weighed 2.67 g. and melted at 190–195°. This crude material was dissolved in 100 ml. of methanol; the solution was filtered and treated with a solution of 2 ml. of concd. sulfuric acid in 20 ml. of water. The solution was then refluxed for one-half hour during which time the color changed to deep violet. It was then poured into one liter of water and extracted with ether. The extract was washed well with water, dried and concentrated. The residue upon crystallization from ether–petroleum ether (b. p. 35–60°) gave 1.38 g. (67%) of crystalline material melting at 200–208° after softening somewhat lower. Recrystallization from acetone yielded material (1.05 g.) melting at 210–215°. Further recrystallization from acetone gave diamond-shaped plates melting at 213–215°; $[\alpha]^{22}D$ + 97.2 (9.9 mg. made up to 2 ml. with chloroform, $\alpha D$ − 0.481°, *l*, 1 dm.); $\epsilon_{240}$ − 17,800 (methanol).

*Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.07; H, 9.05.

In one experiment, the intermediate **ketal** of 17α-hydroxyprogesterone (V) was purified. Several recrystallizations from methanol gave fine, white plates melting at 212–216°.

*Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.76; H, 9.02.

No improvement in yield of 17α-hydroxyprogesterone was obtained by conducting the hydrolysis at room temperature for two hours or by purifying the intermediate ketal.

## Summary

A new partial synthesis of 17α-hydroxyprogesterone is described.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 16, 1949

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE, LONDON]

# Stereochemistry of the Cholesterol Dichlorides[1]

BY D. H. R. BARTON* AND E. MILLER

During the last twenty years, intensive study of the stereochemistry of steroidal compounds has led to solution of many of the important problems in this field.[2] It is generally agreed that the determination of the stereochemistry of halogen derivatives is more difficult than that of the corresponding hydroxylic compounds. This is illustrated in the steroid field by the relatively recent solution[3,4] of the problem of the orientation of the cholesteryl and cholestanyl 3-halides, as compared with the long accepted configurations of the corresponding 3-alcohols. Again the stereochemistry of the 5,6-dihydroxy-derivatives of cholestanol is known with certainty,[2] but the configurations of the corresponding dihalides have not hitherto been elucidated.

In order to remedy this deficiency in our knowledge attention was first directed to the two cholesterol dichlorides. One of these, which is readily obtained by the addition of chlorine to cholesterol[5] (or better, the corresponding esters), has been known for many years.[6] Its method of formation implies that it must be a *trans*-dichloride[7] and this is confirmed[8] by its resistance to dehydrochlorination on refluxing with methanolic caustic potash. The second dichloride of cholesterol was first prepared (as the benzoate) by Berg and Wallis[9] by the action of iodobenzene dichloride[10] on cholesteryl benzoate. It was shown by these authors that alkaline reagents provoked a facile elimination of hydrogen chloride, an observation that we have fully confirmed, there being formed 6-chlorocholest-5-en-3β-ol. Since the molecular rotation differences recorded by Berg and Wallis for the acylation of the latter were not in good agreement with those expected, we have redetermined the relevant rotations (Table I) and have found that, in fact, the agreement for the constitution assigned is satisfactory. The behavior of the new cholesterol dichloride benzoate is best explained if the two chlorine atoms are in the *cis*-relationship. At first we were unable to obtain reproducible results during its preparation using the iodobenzene dichloride reagent. Instead of the *cis*-dichloride benzoate of Berg and Wallis the ordinary *trans*-dichloride benzoate was isolated. In the end it was discovered that the reagent can react by two different mechanisms, both of which lead to the addition of two chlorine atoms to the

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(1) This paper is Part XIV in our series on the "Application of the Method of Molecular Rotation Differences to Steroids." It was supported, in part, by a Research Grant from the Chemical Society, London.

(2) See "Natural Products Related to Phenanthrene," by L. F. Fieser and M. Fieser, 3rd edition, especially Chapter X (by R. B. Turner).

(3) Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946).

(4) Dodson and Riegel, *J. Org. Chem.*, **13**, 424 (1948); compare E. Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937).

(5) For an improved preparation of the benzoate see Exptl. section.

(6) Mauthner, *Monatsh.*, **15**, 85, 362 (1894); **27**, 421 (1906).

(7) *Inter alia*, Michael, *J. prakt. Chem.*, **52**, 344 (1895); McKenzie, *J. Chem. Soc.*, **101**, 1196 (1912); Terry and Eichelberger, THIS JOURNAL, **47**, 1067 (1925); Roberts and Kimball, *ibid.*, **59**, 947 (1937); Lucas and Gould, *ibid.*, **63**, 2541 (1941).

(8) Hückel, Tappe and Legutke, *Ann.*, **543**, 191 (1940); Cristol, THIS JOURNAL, **69**, 338 (1947); compare Hughes, Ingold, *et al.*, *J. Chem. Soc.*, 2093 (1948).

(9) Berg and Wallis, *J. Biol. Chem.*, **162**, 683 (1946).

(10) Garvey, Halley and Allen, THIS JOURNAL, **59**, 1827 (1937).

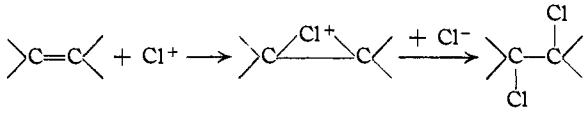
TABLE I

| | $[M]_D$[a] Alcohol | Acetate | Benzoate | $\Delta_1$ | $\Delta_2$ |
|---|---|---|---|---|---|
| Cholest-5-en-3β-ol[b] | −154 | −188 | − 74 | −34 | + 80 |
| 6-Chlorocholest-5-en-3β-ol (see Exptl. section) | −175 | −232 | − 79 | −57 | + 96 |
| 6-Chlorocholest-5-en-3β-ol (Berg and Wallis) | −265 | −190 | −105 | +75 | +160 |

[a] All rotations in chloroform. [b] Barton and Cox, *J. Chem. Soc.*, 783 (1948).

ethylenic linkage. The first of these occurs preferentially to the second in the presence of small amounts of water.[11] Since it furnishes the *trans* dichloride it must proceed by an ionic mechanism such as is represented by the scheme (A). The effect of water on the ratio of the two dichlorides formed in the reaction is illustrated in Table II. The second mechanism was studied by Bloom-

$$C_6H_5ICl_2 + H_2O \longrightarrow C_6H_5I + HCl + HOCl$$
$$(\equiv C_6H_5I + H^+ + Cl^- + OH^- + Cl^+)$$



$$H^+ + OH^- \longrightarrow H_2O \ldots\ldots \text{then repeat cycle}$$

Scheme (A)

TABLE II

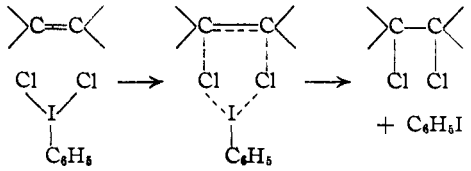
| Molar ratio of cholesteryl benzoate–water | Yield of dichloride % 5α,6α- | % 5α,6β- |
|---|---|---|
| ∞ | 83 | 15 |
| 7:1 | 22 | 60 |
| 1:1 | 9 | 64 |

field[12] when he examined the reaction of iodobenzene dichloride on rubber. The main product was one of *addition* rather than *substitution*, which is the normal process with molecular chlorine. Since the latter reaction is ionic in character[13] Bloomfield's evidence amounts to a proof that the iodobenzene dichloride reaction, under anhydrous conditions, cannot have a similar mechanism. Bloomfield concluded that the reaction was of a free radical chain type involving chlorine atoms, for, although the process was not catalyzed by peroxide, it was said to be retarded by the addition of quinol and then gave mainly *substitution*. In fact, since quinol is hydroxylic, this was probably merely a demonstration of the iodobenzene dichloride reacting as an ionic reagent according to scheme (A). It does not constitute proof of a radical mechanism. We regard the reaction as possibly proceeding by straightforward molecular interaction as illustrated in scheme (B). A consequence of this would be that *cis*-stereochemistry of the added chlorine atoms would be guaranteed.

(11) Compare Décombe and Rabinowitch, *Compt. rend.*, **225**, 583 (1947).

(12) Bloomfield, *J. Chem. Soc.*, 114 (1944).

(13) Taft, THIS JOURNAL, **70**, 3364 (1948).



Scheme (B)

The evidence discussed thus far may be taken as proving that ordinary cholesterol dichloride is 5α,6β- or 5β,6α- and that the *cis*-dichloride is 5α,6α- or 5β,6β-dichlorocholestanol. In order to distinguish between these possibilities the two cholesterol dichlorides[14] were oxidized to the corresponding ketones, both of which readily lost hydrogen chloride on treatment with sodium acetate in ethanolic solution. The products of these reactions were the two stereoisomeric 6-chloro-$\Delta^4$-cholesten-3-ones, which were easily crystallized and manipulated at temperatures not above 30°. Their formulation is justified by their absorption spectra (which exclude the alternative 4-chlorocholest-4-en-3-one structure), by their method of preparation[15] and by further transformations described below.

Since different ketones are formed when the asymmetry at $C_5$ is destroyed, the two cholesterol dichlorides must have the same configuration at this center. An assignment of configurations at both centers comes from a consideration of molecular rotation differences. In the cholestane series 6α-hydroxy- and -acetoxy- compounds are more dextrorotatory than the corresponding 6β-hydroxy- and -acetoxy-derivatives[16] and the same applies to the derivatives of $\Delta^4$-cholestene listed in Table III. Now the optical activity of a halide is often comparable with that of the corresponding alcohol[17] and thus a pair of stereoisomeric halides usually preserve the same sign for the difference in molecular rotation as do the pair of alcohols of corresponding configuration. The investigations of the 3-halides from cholestanol, briefly referred to above, are an example of this generalization.[18]

(14) For an improved preparation of the *cis*-dichloride of cholesterol see Exptl. section.

(15) Compare the formation of 6-bromocholest-4-en-3-one: Ruzicka, *et al.*, *Helv. Chim. Acta*, **19**, 1147 (1936); Dane, Wang and Schulte, *Z. physiol. Chem.*, **245**, 80 (1937).

(16) Barton and Klyne, *Chem. and Ind.*, 755 (1948).

(17) *Inter alia*, Kenyon, Phillips and Pittman, *J. Chem. Soc.*, 1072 (1935); Hughes, Ingold, *et al.*, *ibid.*, 1252, 1208 (1937); Levene and Rothen, *J. Biol. Chem.*, **127**, 237 (1939); Stevens and McNiven, THIS JOURNAL, **61**, 1295 (1939).

(18) In the literature there is an apparent discrepancy with regard to the 6-position. Thus it is stated (Sobotka, "The Chemistry of the Sterids," Ballière, Tindall and Cox, 1938) that treatment of cholestan-6α-ol ($[\alpha]_D$ +35°) with phosophorus pentachloride afforded a 6-chlorocholestane, m. p. 147°, $[\alpha]_D$ +45°. This would imply that the reaction proceeded without inversion, which is contrary to the correlations established by Shoppee (*J. Chem. Soc.*, 1138, 1147 (1946)). In actual fact reference to the original literature (Stange, *Z. physiol. Chem.*, **220**, 34 (1933)) shows that the rotation was recorded as positive in the theoretical part of the paper, but that the actual angle read, in the experimental section, was *negative*. The corrected rotation of $[\alpha]_D$ −45° is in satisfactory agreement with that to be expected for 6β-chlorocholestane. The action of thionyl chloride on cholestan-6α-ol should according to Shoppee, furnish the

The 6-chlorocholest-4-en-3-one from the *cis*-dichloride is much more dextrorotatory (Table III) than that from the *trans*-dichloride and therefore the dichlorides must be formulated as 5α,6α- and 5α,6β-, respectively.

TABLE III

| Substance | $[M]_D$[a] 6β- | 6α- | $\Delta([M]_D\ 6\alpha - [M]_D\ 6\beta)$ |
|---|---|---|---|
| Cholestan-3β,6-diol[b] | + 57 | +154 | + 97 |
| Cholestan-3β,6-diol diacetate[b] | −117 | +195 | +312 |
| Δ⁴-Cholesten-3β,6-diol[c,d] | + 32[e] | +117 | + 85 |
| Δ⁴-Cholesten-3β,6-diol diacetate[c,d] | − 58 | +100 | +158 |
| 6-Chloro-Δ⁴-cholesten-3-one[f] | + 65 | +247 | +182 |
| 5α,6-Dichlorocholestan-3β-ol[f] | −123 | + 9 | +132 |

[a] All rotations in chloroform unless specified to the contrary. [b] Plattner and Lang, *Helv. Chim. Acta*, **27**, 1872 (1944). [c] Prelog and Tagmann, *ibid.*, **27**, 1867 (1944). [d] Prelog, Ruzicka and Stein, *ibid.*, **26**, 2222 (1943). [e] In pyridine. [f] Exptl. section.

A final chemical proof for the configurations assigned was obtained in the following way. Treatment of the known α-oxide of cholesterol with hydrogen chloride afforded 5α-hydroxy-6β-chlorocholestan-3β-ol,[19] oxidized by chromic acid to the corresponding ketone in an over-all yield of about 80%. Dehydration of the latter with thionyl chloride in pyridine afforded 6β-chlorocholest-4-en-3-one identical in all respects with the compound obtained from ordinary (*trans*)-cholesterol dichloride.[20]

The behavior of the two stereoisomeric 6-chlorocholest-4-en-3-ones mentioned above toward the 2,4-dinitrophenylhydrazine reagent proved to be of interest. On treatment in the *hot* according to the customary procedure the 2,4-dinitrophenylhydrazone of cholesta-4,6-dien-3-one was obtained. The formation of this compound was not unexpected for Djerassi[21] had previously shown that the elimination of hydrogen bromide from analogous 6-bromo-compounds was similarly facilitated.[22] We also found that the same treatment applied to 5α,6β-dichlorocholestan-3-one, to 5α,6α-dichlorocholestan-3-one and to 5α-hydroxy-6β-chlorocholestan-3-one, afforded the same product. Likewise the 2,4-dinitrophenylhydrazones of 5α,6β-dichlorocholestan-3-one and of 5α-hydroxy-6β-chlorocholestan-3-one gave the same product, merely when refluxed gently for a few minutes with dilute alcoholic hydrochloric acid. Of greater interest however was our discovery that both stereoisomeric 6-chlorocholest-4-en-3-ones gave an orange substance, $C_{33}H_{48}N_4O_5$, m. p. 245°, $[\alpha]_D$ *ca.* + 130° (in chloroform), when treated with the 2,4-dinitrophenylhydrazine reagent in the *cold* at less than 20°, no matter whether methanol, ethanol or dioxane was used as solvent. This substance was labile in acid solution and by refluxing with dilute alcoholic hydrochloric acid for a few minutes lost water to give cholesta-4,6-dien-3-one 2,4-dinitrophenylhydrazone. It could be chromatographed over alumina only if all traces of acid or acid-yielding substances had been removed. However, it was stable to alkali. It seems to us that the formulation of this compound may be of importance in the elucidation of the mechanism of the dehydrohalogenation of 6-halogeno-Δ⁴-3-ketones of the steroid series, brought about by the influence of 2,4-dinitrophenylhydrazine.[21,22,23]

The elucidation of the stereochemistry of the cholesterol dichlorides enables configurations to be assigned to a number of other steroid dichlorides, which have been prepared by the straightforward addition of chlorine to the Δ⁵-ethylenic linkage. Examples are cholesteryl chloride dichloride,[24,25] in which the stereochemistry must be 3β,5α,6β-, and cholestene dichloride[26] in which the sterochemistry must be 5α,6β-. These assignments of configuration are supported by the optical rotation evidence.

## Experimental[27]

**5α,6β-Dichlorocholestan-3β-yl Benzoate.**—Twenty-five grams of cholesteryl benzoate,[28] dissolved in 200 ml. of chloroform containing 0.2 g. of antimony trichloride and cooled to −20°, were treated with a chloroform solution of chlorine at the same temperature. The chlorine solution was added slowly until the yellow color was no longer discharged. After washing with sodium carbonate solution, hydrochloric acid and finally water, evaporation of the chloroform and recrystallization from ethyl acetate–

true 6α-chlorocholestane with retention of configuration. This reaction had already been carried out by Professor Sir Ian Heilbron (unpublished observation) and a re-examination of the product showed m. p. 150–151°, $[\alpha]_D$ +51°, in satisfactory agreement with the assigned configuration. We are much indebted to Sir Ian Heilbron for an opportunity to re-examine this substance.

(19) Chakravorty and Levin, THIS JOURNAL, **64**, 2317 (1942), attempted the preparation of this compound by the action of pyridine hydrochloride on the α-oxide, but they reported that it was unstable and lost chlorine on recrystallization. In our hands authentic 5α-hydroxy-6β-chlorocholestan-3β-ol proved to be a stable substance.

(20) A further proof for the formulation of cholesterol *trans*-dichloride as 5α,6β- has already, in effect, been given by Décombe and Rabinowitch (*Bull. soc. chim.*, [V] **6**, 1510 (1939)) who found that catalytic hydrogenation afforded a 6-chlorocholestanol m. p. 136–137°, $[\alpha]_{5461}$ −21°. From the rotation this must be 6β-chlorocholestan-3β-ol.

(21) Djerassi, THIS JOURNAL, **71**, 1003 (1949).

(22) Compare Mattox and Kendall, *ibid.*, **70**, 882 (1948).

(23) The formation of the orange substance m. p. 245° probably explains the observation of Djerassi[21] that treatment of 6-bromo-Δ⁴-3-ones, or of the isomeric 2-bromo- compounds, sometimes gave yellowish-orange colored crystals, which readily afforded the normal bright red crystals on recrystallization.

(24) Mauthner and Suida, *Monatsh.*, **16**, 85 (1894).

(25) Pirrone, *Gazz. chim. ital.*, **62**, 63 (1932).

(26) Mauthner, *Monatsh.*, **27**, 421 (1906).

(27) M. p.'s are not corrected. All specimens were dried *in vacuo* at 20° below their m. p.'s or at 120°, whichever was the lower temperature, before taking the rotation. All rotations are for the sodium D line and in chloroform solution. The measurements were made at room temperature which varied from 15 to 25°. All values of $[\alpha]_D$ have been approximated to the nearest degree. Concentrations (*c*) are expressed in g. per 100 ml. of solution.

Standard chemical operations (acetylations, benzoylations, alkaline hydrolysis) were carried out as in Part IV.[28] Microanalyses are by Drs. Weiler and Strauss, Oxford.

(28) Barton and Cox, *J. Chem. Soc.*, 783 (1948).

methanol furnished (20.44 g., 72%) 5α,6β-dichlorocholestan-3-β-yl benzoate, m. p. 130–131°, $[\alpha]_D$ −20° (*c*, 2.28), $[M]_D$ −112. In the same way there were prepared 5α,6β-dichlorocholestan-3β-ol, recrystallized from ethyl acetate–methanol, m. p. (after drying), 143–144°, $[\alpha]_D$ −27° (*c*, 2.03), $[M]_D$ −123°, and the corresponding acetate, recrystallized from ethyl acetate–methanol, m. p. 89–90°, $[\alpha]_D$ −29° (*c*, 2.08), $[M]_D$ −145°, and 5α,6β-dichlorocholestane, recrystallized from ethyl acetate–methanol, m. p. 121–122°, $[\alpha]_D$ −28° (*c*, 2.09), $[M]_D$ −124°.

Alkaline hydrolysis of dichloroacetate or benzoate also furnished 5α,6β-dichlorocholestan-3β-ol. For example 1.4 g. of the benzoate gave 1.1 g. (97%) of pure alcohol m. p. (after drying at 100°) 143–144°, when refluxed with 1.5 g. of caustic potash in methanol–dioxane solution. Acetylation or benzoylation of the dichloroalcohol in pyridine solution in the usual way gave back the acetate or benzoate without difficulty.

None of the 5α,6β-dichloro derivatives described here, including the 3-ketone (see below), showed mutarotation in chloroform solution at room temperature.

**5α,6β-Dichlorocholestan-3-one.**—One and one-tenth grams of 5α,6β-dichlorocholestan-3β-ol was dissolved in 100 ml. of "Analar" acetic acid at 55° on the water-bath; 250 mg. of chromium trioxide in 1 ml. of water was added and the resulting solution was kept at 55° for three-quarters of an hour. After working up by dilution with water, extraction with ether, washing the extract with sodium carbonate solution and then water, and evaporating at not more than 20° *in vacuo*, a residue was obtained which gave the required dichloroketone (0.63 g., 62%) when crystallized from ethyl acetate–methanol *in the cold*. The ketone softened at 114° and melted with vigorous decomposition at 116–117°, $[\alpha]_D$ −27° (*c*, 4.24), $[M]_D$ −123°.

*Anal.* Calcd. for $C_{27}H_{44}Cl_2O$: Cl, 15.5. Found: Cl, 15.65.

On treatment with 2,4-dinitrophenylhydrazine in ethyl alcoholic hydrochloric acid solution in the *cold* 5α,6β-dichlorocholesten-3-one furnished a yellow dinitrophenylhydrazone, recrystallized from chloroform–methanol, m. p. 225° dec. It showed $\lambda_{max.}$ 366 mμ, ε = 25,400, in chloroform.

*Anal.* Calcd. for $C_{33}H_{48}Cl_2N_4O_4$: Cl, 11.2. Found: Cl, 11.75

However on boiling with the 2,4-dinitrophenylhydrazine reagent, as in the usual method of preparing 2,4-dinitrophenylhydrazones, or by boiling the yellow dinitrophenylhydrazone (prepared as above), with alcoholic hydrochloric acid for several minutes, the 2,4-dinitrophenylhydrazone of cholesta-4,6-dien-3-one was obtained.[29]

On heating 0.1117 g. of 5α,6β-dichlorocholestan-3-one at the m. p. *in vacuo* it was found that 0.00021 g. equiv. of hydrogen chloride was evolved (calcd. for 1 g. equiv. per mole of ketone, 0.000245 g. equiv.). The residual gum readily gave the 2,4-dinitrophenylhydrazine derivative, m. p. 245°, described below.

**6β-Chlorocholest-4-en-3-one.**[15]—Five and one-half grams of 5α,6β-dichlorocholestan-3-one was suspended in 250 ml. of ethanol; 6 g. of fused, anhydrous sodium acetate was added and the whole refluxed for one-half hour. Dilution with water gave a white solid which was filtered off and crystallized in the *cold* from ethyl acetate–methanol to give 3.25 g., 64% of 6β-chlorocholest-4-en-3-one, m. p. 129–130° dec., $[\alpha]_D$ + 14° (*c*, 2.32), + 17° (*c*, 1.13), $[M]_D$ + 65°. It showed $\lambda_{max.}$ 241 mμ, ε = 15,100, in alcohol.

*Anal.* Calcd. for $C_{27}H_{43}ClO$: Cl, 8.45. Found: Cl, 8.5.

On one occasion chromatography of 5α,6β-dichlorocholestan-3-one (see above) over Birlec alumina, which is alkaline in reaction, furnished 6β-chlorocholest-4-en-3-one identical in all respects with the compound described above.

**2,4-Dinitrophenylhydrazine Derivative of 6β-Chlorocholest-4-en-3-one.**—Treatment of 6β-chlorocholest-4-en-3-one with the 2,4-dinitrophenylhydrazine reagent in the usual way (in the *hot*) gave the 2,4-dinitrophenylhydrazone of cholesta-4,6-dien-3-one, but mixing ethanolic, methanolic or dioxane solutions in the *cold* (15°) of the reagent, with added aqueous hydrochloric acid, and the ketone (in the same solvent) gave an orange ppt. After freeing from all traces of acid this was purified by chromatography[31] over alumina followed by slow crystallization from chloroform–methanol, to give orange plates, m. p. 245° dec., $[\alpha]_D$ + 130 ± 20° (*c*, 1.01), $\lambda_{max.}$ 382 mμ, ε = 29,800, in chloroform.

*Anal.* Calcd. for $C_{39}H_{48}N_4O_6$: C, 68.25; H, 8.33; N, 9.65; Cl, 0. Found: C, 68.3; H, 8.3; N, 9.9; Cl, 0.

On admixture with the 2,4-dinitrophenylhydrazone of cholesta-4,6-dien-3-one the m. p. was depressed to 204° dec. On boiling for several minutes with ethanol containing a little aqueous hydrochloric acid, the orange compound was smoothly rearranged to this dinitrophenylhydrazone. On the other hand boiling with methanolic caustic potash caused no change.

**5α,6α-Dichlorocholestan-3β-yl Benzoate.**—This was prepared following the general directions of Berg and Wallis.[9] As emphasized in the text, where yields are discussed, the absence of all traces of water is essential for success. Purified by slow crystallization (needles) from chloroform–ethyl acetate, 5α,6α-dichlorocholestan-3β-yl benzoate had m. p. 248–249° dec., $[\alpha]_D$ + 12° (*c*, 5.54). In those experiments where the isomeric 5α,6β-dichloro-compound was produced at the same time the two compounds were roughly separated by digestion with warm alcohol, the 5α,6α-isomer being almost insoluble. The yields quoted in the text are based on this procedure.

Two and one-tenth grams of 5α,6α-dichlorocholestan-3β-yl benzoate was hydrolyzed by refluxing with 5 *N* ethanolic sulfuric acid for twenty hours. Removal of the sulfuric acid and separation from unchanged benzoate by chromatography afforded 1.06 g., 62%, of 5α,6α-dichlorocholestan-3β-ol, recrystallized from ethyl acetate–light petroleum, m. p. 171.5–172.5° dec., $[\alpha]_D$ + 2° (*c*, 0.89), $[M]_D$ + 9°. "Décombe and Rabinowitch" prepared this alcohol, for which they gave m. p. 165–167°, by the controlled alkaline hydrolysis of the corresponding formate. Our method seems superior.

5α,6α-Dichlorocholestan-3β-ol was also prepared by heating the corresponding benzoate with *n*-propanol, saturated with hydrogen chloride, at 180° in a sealed tube for twenty-four hours, but the yields were inferior and careful chromatography was needed for purification.

**6-Chlorocholest-5-en-3β-ol.**[9,32]—One and two-tenths grams of the above-mentioned benzoate was refluxed with excess caustic potash in methanol–dioxane solution for one hour. Working up in the usual way gave 6-chlorocholest-5-en-3β-ol (yield almost quantitative) recrystallized from aqueous ethanol, m. p. 156°, $[\alpha]_D$ −42° (*c*, 1.12), $[M]_D$ −175°. Acetylation afforded the corresponding acetate, recrystallized from ethyl acetate–ethanol, m. p. 131°, $[\alpha]_D$ −50° (*c*, 1.69), $[M]_D$ −232°, while benzoylation furnished the corresponding benzoate, recrystallized from chloroform–ethanol, m. p. 206.5°, $[\alpha]_D$ −15° (*c*, 3.15), $[M]_D$ −79°.

(29) In each case in this paper where this compound is mentioned, it was purified by chromatography over alumina followed by slow crystallization from chloroform–methanol. Isolated in this way it formed very dark red needles, m. p. 232° dec., $\lambda_{max.}$ 309 and 405 mμ, ε = 18,600 and 37,100 respectively, in chloroform, and gave no depression in m. p. on admixture with an authentic specimen of the same m. p. and absorption spectrum kindly supplied by Dr. H. B. Henbest.[30]

(30) Compare Petrow, *J. Chem. Soc.*, 66 (1940).

(31) The precaution of removing every trace of acid is essential. Otherwise chromatography merely leads to the isolation of the 2,4-dinitrophenylhydrazone of cholesta-4,6-dien-3-one. Even so we have found it necessary to use Savory and Moore's standardized alumina for the purification, as other brands also tended to cause this rearrangement in spite of the apparent removal of all acid.

(32) These experiments were carried out by Dr. J. D. Cox.

*Anal.* Calcd. for $C_{34}H_{50}Cl_2O_2$: C, 77.6; H, 9.5; Cl, 6.7. Found: C, 77.5; H, 9.2; Cl, 6.5.

**6α-Chlorocholest-4-en-3-one.**—770 mg. of 5α,6α-dichlorocholestan-3β-ol (see above), dissolved in 100 ml. of "Analar" acetic acid, were oxidized by the addition of 124 mg. of chromium trioxide in a little water, at 40° on the water-bath for one hour. The 5α,6α-dichlorocholestan-3-one thus produced was isolated as for the corresponding 5α,6β-dichloro-compound (see above), but it proved to be rather unstable. It was, therefore, at once treated with sodium acetate as for the preparation of the 6β-chloro-compound (see above). Crystallization of the product in the *cold* from ethyl acetate–methanol afforded 6α-chlorocholest-4-en-3-one, m. p. 125–126°, $[\alpha]_D$ + 61° (*c*, 3.91), + 57° (*c*, 2.73); $[M]_D$ + 247°, $\lambda_{max.}$ 239 mμ, ε = 19,000, in alcohol, giving a large depression in m. p. on admixture with the 6β-isomer.

*Anal.* Calcd. for $C_{27}H_{45}ClO$: Cl, 8.45. Found: Cl, 8.4.

Treatment of 6α-chlorocholest-4-en-3-one with the 2,4-dinitrophenylhydrazine reagent in the *cold* gave the same orange compound m. p. 245°, identified by mixed m. p., rotation ($[\alpha]_D$ + 162 ± 20° (*c*, 0.16)) and $\lambda_{max.}$ 383 mμ, ε = 32,100 in chloroform, as was obtained in the same way from the 6β-isomer (see above), but in the *hot* the 2,4-dinitrophenylhydrazone of cholesta-4,6-dien-3-one was formed. The latter was obtained in the same way from 5α,6α-dichlorocholestan-3-one.

**Cholest-5-en-3β-yl Benzoate α- and β-Oxides.**—The α-oxide, m. p. 166–168°, was readily prepared following the directions of Spring and Swain[33] and separated from the α,β-oxide, m. p. 151.5–152.5°, $[\alpha]_D$ ± 0° (*c*, 2.64), by triangulation from ethyl acetate–methanol. 1.90 g. of the α,β-oxide was resolved by chromatography[34] over alumina (Birlec, Grade H) to give 1.16 g. of benzoate β-oxide, recrystallized from ethyl acetate–methanol, m. p. 171.5–172.5°, $[\alpha]_D$ + 13° (*c*, 3.69), as well as 0.62 g. of the benzoate α-oxide (more difficultly eluted).

On treatment with dry hydrogen chloride in chloroform solution the benzoate β-oxide afforded 5α-chloro-6β-hydroxycholestan-3β-yl benzoate,[35] recrystallized (plates) from ethyl acetate–methanol, m. p. 207–208°.

Similarly the benzoate α-oxide furnished 5α-hydroxy-6β-chlorocholestan-3β-yl benzoate,[36] m. p. 202–203° dec., $[\alpha]_D$ −20° (*c*, 4.45).

**Cholest-5-en-3β-ol α-Oxide and Derivatives.**—Alkaline hydrolysis of the benzoate α-oxide furnished cholest-5-en-3β-ol α-oxide, recrystallized from ethyl acetate–methanol, m. p. 144–145°. On treatment with dry hydrogen chloride in chloroform solution the latter afforded 5α-hydroxy-6β-chlorocholestan-3β-ol, recrystallized from ethyl acetate–methanol; m. p. (after drying *in vacuo*) 173–174°, $[\alpha]_D$ −8° (*c*, 0.92), in almost quantitative yield.

*Anal.* Calcd. for $C_{27}H_{47}ClO_2$: Cl, 8.1. Found: Cl, 8.2.

Oxidation of this alcohol in "Analar" acetic acid with an excess of chromic acid, leaving to stand at room temperature for five hours, gave 5 α-hydroxy-6β-chlorocholestan-3-one, m. p. 216° dec. The ketone was very sparingly soluble in acetic acid and was pptd. during the oxidation in a state of purity (yield 83%).

*Anal.* Calcd. for $C_{27}H_{45}ClO_2$: C, 74.2; H, 10.35; Cl, 8.1. Found: C, 74.2; H, 10.35; Cl, 8.4.

On treatment with the 2,4-dinitrophenylhydrazine reagent in the cold this ketone furnished a yellow 2,4-dinitrophenylhydrazone, purified by chromatography followed by slow recrystallization from chloroform–methanol, m. p. 198–199° dec., $\lambda_{max.}$ 366 mμ, ε = 27,200, in chloroform.

*Anal.* Calcd. for $C_{33}H_{49}ClN_4O_5$: N, 9.1. Found: N, 9.3.

On the other hand treatment with the reagent in the *hot* in the usual way furnished cholesta-4,6-dien-3-one 2,4-dinitrophenylhydrazone which was also obtained in the same way from the yellow 2,4-dinitrophenylhydrazone mentioned above.

As mentioned above 5α-hydroxy-6β-chlorocholestan-3-one decomposed at the m. p. The melt, treated with the 2,4-dinitrophenylhydrazine reagent in the *cold*, gave cholesta-4,6-dien-3-one 2,4-dinitrophenylhydrazone.

Acetylation of 5α-hydroxy-6β-chlorocholestan-3-β-ol in the usual way afforded the corresponding 3-acetate, recrystallized from ethyl acetate–methanol, m. p. 188–189° dec., $[\alpha]_D$ −35° (*c*, 3.26). Spring and Swain[33] give m. p. 186–187°, $[\alpha]_D$ −27°.

Attempts to remove the elements of water from 5α-hydroxy-6β-chlorocholestan-3-one using thionyl chloride, phosphorus oxychloride in pyridine, acetic anhydride and phosphorus pentoxide all under a variety of conditions, were unsuccessful. In all cases the ketone was recovered unchanged or cholesta-4,6-dien-3-one, characterized as the 2,4-dinitrophenylhydrazone, was produced. Controlled pyrolysis by melting the ketone in intimate admixture with five times its weight of acetanilide at 150–160° for five minutes gave intractable gums in which the presence of 6β-chlorocholest-4-en-3-one was demonstrated by the orange derivative it gave with the 2,4-dinitrophenylhydrazine reagent in the *cold*.

The dehydration was finally accomplished in the following way.[37] Two hundred milligrams of 5α-hydroxy-6β-chlorocholestan-3-one was dissolved in 3 ml. of dry pyridine and cooled to 0°. Three molecular proportions of redistilled thionyl chloride were added dropwise at the same temperature and the mixture was left to stand for ten minutes. It was then poured into water, extracted with ether and worked up in the usual way. Recrystallization from ethyl acetate–methanol in the cold gave 6β-chlorocholest-4-en-3-one, m. p. 129–130°, $[\alpha]_D$ + 13° (*c*, 2.00), undepressed in m. p. by admixture with a specimen of the same m. p. prepared as described above.

**Isoergosterone 2,4-Dinitrophenylhydrazone.**—For comparative purposes this compound was prepared from isoergosterone[38] in the usual way. Purified by chromatography followed by slow crystallization from chloroform–methanol it formed dark-red needles, m. p. 248°, $\lambda_{max.}$ 308 and 400 mμ, ε = 16,700 and 35,900, respectively.

*Anal.* Calcd. for $C_{34}H_{46}N_4O_4$: N, 9.75. Found: N, 10.3.

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## Summary

Ordinary (*trans*) cholesterol dichloride has been shown to have the chlorine atoms in the 5α,6β-configuration. The recently prepared (*cis*) cholesterol dichloride has been proved to possess the 5α,6α-configuration.

Dehydrochlorination of the two 3-ketones corresponding to the above dichlorides afforded two stereoisomeric 6-chloro-Δ⁴-cholesten-3-ones, both of which gave the same orange substance, $C_{33}H_{48}N_4O_5$, when treated with the 2,4-dinitrophenylhydrazine reagent in the *cold*.

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(33) Spring and Swain, *J. Chem. Soc.*, 1356 (1939).

(34) Compare Plattner, Petrzilka and Lang, *Helv. Chim. Acta*, **27**, 513 (1944), who resolved the acetate of α,β-oxide in the same way.

(35) Spring and Swain[33] give m. p. 206–207° decomp., $[\alpha]_D$ ±0° (in chloroform).

(36) Spring and Swain[33] give m. p. 202–203° dec., $[\alpha]_D$ −20° (in chloroform).

(37) Compare Prelog and Tagmann, *Helv. Chim. Acta*, **27**, 1867 (1944).

(38) Barton and Miller, *J. Chem. Soc.*, 337 (1949).